

**In the Specification:**

Please insert the attached Sequence Listing as separately numbered pages after the abstract. This Sequence Listing replaces any previously filed Sequence Listings of the subject application.

***Please replace paragraph 37 on page 8 of the specification with the following paragraph:***

[37] Polymorphisms in TIM sequences are provided in the sequence listing. In mouse TIM-1, these polymorphisms encode three amino acid differences and a fifteen amino acid deletion in HBA/DBA. Polymorphisms in coding regions of human *Tim1* include an insertion (labeled polymorphism 1, allele 3), 157insMTTVP, **SEQ ID NO:38**, observed in 65% of the chromosomes, and a deletion (polymorphism 5), **SEQ ID NO:39**, 195ΔThr, observed in 65% of the chromosomes. Other polymorphisms are 157insMTTVP, T140A (polymorphism 7) **SEQ ID NO:40**; **and single residue polymorphisms** V161A; (polymorphism 2); V167I (polymorphism 3); T172A (polymorphism 4); N258D (polymorphism 6). Polymorphism 4 was observed in 40% of the chromosomes, and the other polymorphisms were each observed in ≤5% of the chromosomes. Most of these variations (2-6) are located within exon 3, the first mucin-encoding exon, and all of the variants occur at the genomic level and are not splice variants.

***Please replace paragraph 42 on page 10 of the specification with the following paragraph:***

[42] In some embodiments, the Tim gene sequence is other than human TIM-1 allele 1, as set forth in the sequence listing. In one embodiment of the invention, the TIM-1 genetic sequence comprises an insertion encoding the amino acids MTTVP (**SEQ ID NO:21, residues 158-163**). In naturally occurring human genomes, this sequence is encoded by the genetic sequence, ATGACAACGACTGTTCCA, **SEQ ID NO:22, bases 472-489**. In combination with HAV seropositivity, this allele is protective for atopy, and therefore the presence of the allele is indicative that an individual may benefit from exposure to HAV for atopy treatment and/or prophylaxis. Determination of the presence of the allele may be determined by various methods known in the art, e.g. hybridization with a polynucleotide specific for the polymorphism.

***Please replace paragraph 43 on page 11 of the specification with the following paragraph:***

[43] The human 157insMTTTVP amino acid sequence is provided (SEQ ID NO:21), and the encoding gene as (SEQ ID NO:22). DNA encoding a 157insMTTTVP amino acid sequence may be cDNA or genomic DNA or a fragment thereof that encompasses the inserted sequence, e.g. ATGACAACGACTGTTCCA, **SEQ ID NO:22, bases 472-489**. The term "ins157 gene", or "polymorphism 1" shall be intended to mean the open reading frame encoding such specific polypeptides, as well as adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 1 kb beyond the coding region, in either direction.

***Please replace paragraph 82 on page 21 of the specification with the following paragraph:***

[82] Polypeptides of particular interest that are fragments of the TIM polypeptides include specific domains of the TIM polypeptides, where a domain may comprise, for example, the extracellular domain, or the domains within the extracellular domain: the mucin domain and/or the Ig domain. Domains may also comprise the cytoplasmic domain, e.g. a fragment encompassing the tyrosine kinase phosphorylation motif, RAEDNIY, **SEQ ID:1, residues 293-299**, the expanded region, SRAEDNIYIVEDRP, **SEQ ID:1 residues 292-305**; the domain comprising the insertion at position 157; etc. Polypeptides encoded by the soluble splice variants are also of interest. Polypeptides are usually at least about 5 amino acids in length, more usually at least about 8 amino acids in length, at least about 12, 15 20, 25, 50 or more amino acids in length, up to the complete protein, and fusion products thereof. The sequence of the Ig domains are as follows: human TIM-1 Ig domain, SEQ ID NO: 17, 19, 21, 23, 25, 27, residues 21-126; human TIM-3 Ig domain, SEQ ID NO: 29 and 31, residues 22-131; human TIM-4 Ig domain, SEQ ID NO: 33 and 35, residues 25-133; mouse TIM-1 Ig domain, SEQ ID NO: 1 and 3, residues 21-129; mouse TIM-2 Ig domain, SEQ ID NO: 7, residues 22-128; mouse TIM-3 Ig domain, BALB/c allele, SEQ ID NO: 9, residues 22-132; mouse TIM-3 Ig domain, DBA/2 allele, SEQ ID No: 11, residues 22-132; mouse TIM-4 Ig domain, SEQ ID NO: 13 and 15, residues 25-135.

***Please replace paragraph 135 on page 36 of the specification with the following paragraph:***

[135] Using cDNA from conA-stimulated splenocytes, we identified and cloned two mouse orthologues of Kim1, which we term Tim1 (SEQ ID NO:1) and Tim2 (SEQ ID NO:5), that map to the Tapr region, as shown in Fig. **5A 5B**. TIM-3 (SEQ ID NO:9) is a third, more distantly related, orthologue of KIM-1.

***Please replace paragraphs 137-138 on page 11 of the specification with the following paragraphs:***

[137] The mouse *Tim1* gene encodes a 305 amino acid membrane protein, that has 78% overall identity with rat KIM-1 and 35% identity with human HAVcr-1. A gapped multiple sequence alignment with mouse TIM-1 (SEQ ID NO:1), rat KIM-1 (SEQ ID NO:54), human HAVcr-1 (SEQ ID NO:17) and African green monkey HAVcr-1 (SEQ ID NO:55), shown in Fig. **5B 5A**, demonstrates the degree of homology between the TIM-1/KIM-1/HAVcr-1 proteins in these species. The cytoplasmic region of TIM-1 contains two tyrosine residues and includes a highly conserved tyrosine kinase phosphorylation motif, RAEDNIY, SEQ ID:1, residues 293-299, which is integral to the predicted Itk and EGFR kinase site of TIM-1, SRAEDNIYIVEDRP, SEQ ID:1 residues 292-305. The mucin domain of TIM-1 has multiple sites for O-linked glycosylation, and there two sites for N-linked glycosylation found in the immunoglobulin domain.

[138] TIM-2, a similar 305 amino acid membrane protein, has 64% identity to mouse TIM-1, 60% identity to rat KIM-1, and 32% identity to hHAVcr-1 (Figure 5A, B). Like TIM-1, TIM-2 has two extracellular N-linked glycosylation sites and a serine, threonine- rich mucin domain with many O-linked glycosylation sites. TIM-2 also has an intracellular tyrosine kinase phosphorylation motif, RTRCEDQVY, SEQ ID NO:5, residues 285-293.

***Please replace paragraphs 166-168 on page 45-50 of the specification with the following paragraphs:***

[166] The human Tim cDNAs, which are the orthologues of murine Tim-3 and Tim-4 were cloned by PCR. The human orthologue of TIM-1 was cloned as HAVcr-1, the cellular receptor for hepatitis A virus. The TIM family genes are immediately adjacent to each other on human chromosome 5, in the order TIM-4, TIM-1, TIM-3, with no intervening genes. There are TIM

pseudogenes on chromosomes 12 and 19. The gene family members are only moderately related. The protein sequences and relationship among the Tim gene family are shown in Figure 7 (**SEQ ID NOs: 1, 5, 9, 13, 17, 29 and 33**).

[167] The cytoplasmic domains of TIM gene family members are the most conserved domain between mouse and human orthologues, e.g., 77% identity between the human and mouse TIM-3 cytoplasmic domains. In contrast, the whole TIM-3 is only 63% identical between human and mouse. Each TIM gene contains a distinct predicted tyrosine signaling motif. The cytoplasmic region of TIM-1 contains two tyrosine residues and includes a highly conserved tyrosine kinase phosphorylation motif, RAEDNIY (**SEQ ID:1, residues 293-299**). The expanded region, SRAEDNIYIVEDRP (**SEQ ID:1 residues 292-305**) contains a predicted site for Itk and EGF receptor phosphorylation. Itk is known to phosphorylate phospholipase C- $\gamma$  (PLC- $\gamma$ ), and thereby trigger a cascade of signaling events that are involved in T cell activation and helper T cell differentiation. Furthermore, Itk signaling affects Th1/Th2 differentiation, and Itk<sup>-/-</sup> mice do not develop strong Th2 responses. EGF receptor kinase activity is associated with cell survival and resistance to cell death. Similarly, TIM-3 contains distinct, conserved tyrosine phosphorylation and SH2 binding motifs in the cytoplasmic domain. This suggests that the interaction of a TIM with its ligand will engage an intracellular signaling pathway and that each TIM will be distinct in this signaling.

[168] The extracellular IgV domain of the TIM proteins also contains a predicted integrin-binding motif that is similar to the SVVYGLR, **SEQ ID NO:58**, motif of osteopontin that is involved in adhesion via alpha(9)beta(1), alpha(4)beta(1), and alpha(4)beta(7) integrins. TIM-1 transfected pre-B cells of the 300.19 line demonstrate a high degree of adhesion and increased survival in cell culture, as compared to non-transfected 300.19 cells. TIM-1 and TIM-2 transfected CHO cells also demonstrate enhanced survival compared to untransfected CHO cells. These results demonstrate that the TIM proteins regulate cell adhesion and death

***Please replace paragraph 172 on page 47 of the specification with the following paragraph:***

[172] After sequencing *Tim1* from the chromosomes from 35 individuals (70 chromosomes) several polymorphisms in *Tim1* were identified, which are shown in Figure 8. These polymorphisms are numbered 1-7 (left column). The full sequence of human TIM-1, which is listed in the NCBI database (NM\_012206), is provided in Figure 8 as a reference point (**SEQ ID**

**NO: 56**). This sequence is present in less than 20% of the chromosomes that were sequenced, due to the existence of multiple, prevalent sequence polymorphisms in the coding region. 6 additional sequence variations were identified, shown in Figure 8, and all of the polymorphisms were observed in the mucin, extracellular domain, as was true for mice, although the specific variations were distinct from those seen in mice. Importantly, there is a limited degree of association between these variants, in various combinations. The most pronounced variations are the insertion labeled polymorphism 1, 157insMTTTP (SEQ ID NO: 57), which was observed in 65% of the chromosomes, and the deletion in polymorphism 5, 187ΔThr, was observed in 65% of the chromosomes. Polymorphism 4 was observed in 40% of the chromosomes, and the other polymorphisms were each observed in ≤5% of the chromosomes. Notably, most of these variations (2-6) are located within exon 3, the first mucin-encoding exon, and all of the variants occur at the genomic level and are not splice variants.